Applying 'Patient Blood Management' in the trauma center

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Abstract: PURPOSE OF REVIEW: The purpose of this review is to highlight the use of tranexamic acid, point-of-care testing, algorithm-based treatment of trauma-associated coagulopathy with factor concentrates to reduce blood loss and transfusion requirements in order to improve outcome. In addition, the management of patients on new oral anticoagulants, drugs with renewed interest and the tolerance of relatively low hemoglobin levels in the context of trauma will be discussed. RECENT FINDINGS: Early administration of tranexamic acid reduces mortality without increasing the risk of thromboembolic events. Point-of-care testing is increasingly recommended. Goal-directed individualized coagulation algorithms with the use of factor concentrates allow reducing the amount of allogeneic blood products to be administered. Treatment of trauma patients with one of the new oral anticoagulants is challenging. Furthermore, new mechanisms have been discovered such as deep neuromuscular blockade to better tolerate acute anemia. SUMMARY: Applying Patient Blood Management concept to the trauma patient is possible and efficacious. Antihyperfibrinolytics such as tranexamic acid, point-of-care testing and coagulation algorithms with the use of factor concentrates allow a reduction of the number of transfusions, the costs and will likely ameliorate outcome of major trauma patients.

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Recent findings
Early administration of tranexamic acid reduces mortality without increasing the risk of thromboembolic events. Point-of-care testing is increasingly recommended. Goal-directed individualized coagulation algorithms with the use of factor concentrates allow reducing the amount of allogeneic blood products to be administered. Treatment of trauma patients with one of the new oral anticoagulants is challenging. Furthermore, new mechanisms have been discovered such as deep neuromuscular blockade to better tolerate acute anemia.

Summary
Applying Patient Blood Management concept to the trauma patient is possible and efficacious. Antihyperfibrinolytics such as tranexamic acid, point-of-care testing and coagulation algorithms with the use of factor concentrates allow a reduction of the number of transfusions, the costs and will likely ameliorate outcome of major trauma patients.

Keywords
goal-directed transfusions, Patient Blood Management, ROTEM, thromboelastometry, transfusion management, traumatic coagulopathy

INTRODUCTION

Trauma-associated bleeding leading to death has been reported in up to 40% of all casualties in civilian trauma centers [1,2,3▪▪]. Furthermore, it is assumed that up to one-quarter of trauma-associated deaths might be preventable if early and rapid control of blood loss and coagulopathy is established [4,5▪▪]. Injuries leading to exsanguination are to be located in the majority of the cases in the thorax, abdomen and pelvis [6]. In addition, prognosis of these patients is worse when coagulopathy is present at hospital admission [7–11]. For this reason, early, aggressive, and rapid hemostatic interventions are the key to prevent exsanguination and avoid or minimize massive transfusion requirements [3▪▪].

Since 2010 the World Health Organization urges member states to utilize transfusion alternatives and develop individualized Patient Blood Management Programs in order to reduce transfusion needs. The three pillars of Patient Blood Management consist of: 'detection and treatment of preoperative anemia, reduction in perioperative red blood cell loss, and harnessing and optimizing the patient-specific physiological reserve of anemia (including restrictive hemoglobin transfusion triggers)' [12▪,13▪,14▪▪,15▪,16▪▪].

The first pillar is obviously not applicable in the context of trauma, but the second and third pillars are to be used also in the case of trauma. Standard coagulation tests are used widely to

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KEY POINTS

- The second and third pillar of Patient Blood Management Programs can be applied in the setting of trauma patients to reduce the use of blood products.
- The use of new oral anticoagulants is a new challenge in trauma, as reversal of these drugs is difficult and partially impossible.
- Tranexamic acid is becoming one of the key drugs to reduce bleeding and reduce mortality in trauma patients.

identify trauma-induced coagulopathy but the value of these tests has been challenged in recent years. Routine coagulation tests were not developed to identify bleeding in trauma. Furthermore these tests are neither predictive for bleeding nor validated for use in patients with major trauma [17]. For this reason point-of-care devices, such as rotational thromboelastometry (ROTEM, TEM Innovations GmbH, Munich, Germany) or thromboelastography (TEG, Haemonetics Corp, Niles, IL, USA), are used increasingly to treat bleeding in trauma and are actually recommended to assist in characterizing the coagulopathy and guide the hemostatic therapy [3▪▪,18–21,22▪▪].

The purpose of this review is to highlight the use of tranexamic acid, point-of-care testing, algorithm-based treatment of trauma-associated coagulopathy with factor concentrates to reduce blood loss and transfusion requirements in order to improve outcome. In addition, the management of patients on new oral anticoagulants, drugs with renewed interest and the tolerance of relatively low hemoglobin levels in the context of trauma will be discussed.

TRANEXAMIC ACID

In 1950, Okamoto *et al.* [23] described for the first time the lysin derivate tranexamic acid (trans-4-aminomethylcyclohexane-1-carboxylic acid, TXA) that inhibits the action of plasmin. The use of TXA showed a significant blood sparing effect in elective surgery [24]. In 2010, the CRASH-2 Study was the first randomized, placebo-controlled trial to investigate TXA use in trauma. Application of TXA to adult trauma patients in the emergency department reduced all-cause mortality from 16.0 to 14.5% ($P = 0.0035$) and the risk of death due to blood loss from 5.7 to 4.9% ($P = 0.0077$). The dosing regimen was 1 g intravenously (i.v.) over 10 min followed by an infusion of 1 g over 8 h. Expected severe side-effects, in particular thrombotic events such as myocardial infarction and vascular occlusive events were specifically assessed and found to occur less frequently in the tranexamic acid group [25]. This study led to a worldwide increased scientific interest for this antifibrinolytic drug (2009: 84 PubMed listed publications, January–October 2013: 229 publications. Keyword: tranexamic acid).

Recent studies review dose, timing of application, exact indication and potential contraindications or adverse events of TXA use in trauma patients. Grassin-Delyle *et al.* [26▪] proposed a dosing scheme of TXA based upon a pharmacokinetic open two-compartment model with linear elimination. This implicates bolus application with continuous infusion of TXA. The validity for trauma patients may be limited as the calculations were made with children on cardiopulmonary bypass. A systematic review of 104 randomized trials found that the highly significant reduction of surgical blood loss was largely independent of the i.v. TXA doses from 5.5 to 300 mg/kg. The authors conclude that a total dose of 1 g is sufficient for most adult patients [27,28▪▪].

In the prehospital setting 40 trauma patients received TXA: 55% of the victims had penetrating injuries, 45% had blunt trauma. The authors concluded that prehospital administration of TXA at the site of injury is feasible and that no direct adverse drug events were observed [29▪▪]. However, the study design and sample size did not allow assessing patient's outcome [29▪▪]. The re-analysis of the CRASH-2 data showed that early TXA administration within 1 h of arrival in the emergency room significantly reduced the risk of death due to bleeding from 7.7 to 5.3% and from 6.1 to 4.8% when given within 1–3 h. Later administration resulted in an increased mortality due to bleeding (4.4 vs. 3.1%) [30]. Moreover, the use of TXA has been shown to be highly cost-effective [31▪▪].

TXA had also been successfully introduced in military treatment algorithms. Despite greater Injury Severity Scores after suffering combat injuries, mortality was lowest for patients receiving cryoprecipitate and TXA (11.6%, $n = 168$) and TXA only (18.2%, $n = 148$) compared with cryoprecipitate alone (21.4%, $n = 258$) or no cryoprecipitate/TXA (23.6%, $n = 758$). In addition, a systematic Cochrane review provides evidence that TXA reduces blood transfusions in patients requiring emergency or urgent surgery [32▪].

On the basis of WHO data and systematic literature review, Ker *et al.* [28▪▪] estimated that approximately 400 000 trauma patients die in hospital due to bleeding. They calculated that approximately 128 000 deaths might be averted if these patients received TXA within 1–3 h of injury.

In accordance with the European trauma treatment guideline for the management of bleeding and coagulopathy following major trauma, 'we emphasize that the first dose of TXA should be given to all patients with trauma and significant bleeding prehospitally at the scene of accident or at the latest within 3 h after the initial trauma' [3▪▪].

POINT-OF-CARE TESTING

In trauma, coagulopathy is common and multifactorial. Early recognition and treatment is likely to reduce blood loss, the use of blood products, and morbidity and mortality [3▪▪,33,34]. In recent publications, transfusion algorithms guided goal-directed transfusion (Fig. 1) therapy based on laboratory variables and point-of-care testing were described [3▪▪,35]. Thromboelastography and thromboelastometry both measure and graphically display the changes in viscoelasticity at all stages of the developing and resolving clot, and provide the first results within 5–10 min, whereas laboratory values take from 30 min and up to 90 min delaying treatment in patients [36]. The method of the ROTEM has been described in detail elsewhere [37].

To monitor coagulation in the trauma patient, various tests are available including International Normalized Ratio, aPTT, thrombin time, fibrinogen testing (often by the Clauss method) [38], platelet count, platelet function testing, and factor XIII and FVIII determination. Proof-of-concept monitoring of blood coagulation at the bedside is not only desirable, but is becoming increasingly recommended [3▪▪].

ACUTE ANEMIA

In contrast to routine cases, trauma patients undergoing surgery are generally not accessible for preoperative correction of anemia. However, severe anemia (hemoglobin as low as 14 g/l) can be survived without squeal, even without allogeneic blood transfusion [39]. Nevertheless, the European trauma treatment guidelines recommend a hemoglobin target range of 70–90 g/dl [3▪▪].

In a recent trial, pigs were randomized into three different groups and hemodiluted with hydroxyethyl starch comparing no hemodilution vs. hemoglobin of 4.0 g/dl and vs. the critical hemoglobin level of 2.7 g/dl. In the hemodiluted state, 10 mg/kg of pimonidazole was injected, which forms protein adducts in hypoxic cells. Interestingly, metabolic parameters and oxygen consumption did not show that tissue oxygenation was restricted before reaching a hemoglobin level of 2.7 g/dl. Kidneys and skeletal muscle showed enhanced pimonidazole binding and vascular endothelial growth factor expression at a hemoglobin level of 4 g/dl. Other organs like heart, brain and liver showed no signs of tissue hypoxia at hemoglobin levels of 4 g/dl. Acute anemia tolerance is thus organ specific and needs to be further elucidated [40▪▪].

Another interesting finding was made by Pape *et al.* [41▪] showing that deep neuromuscular blockade increases the tolerance of acute normovolemic anemia. The possible mechanism seems to involve a reduction of skeletal muscular oxygen consumption for the benefit of vital organs. Neuromuscular blockade therefore might play an important role in the treatment of trauma victims as critical levels of hemoglobin may be better tolerated.

COAGULATION FACTOR CONCENTRATES

The transfusion of fresh frozen plasma (FFP) leads to adverse effects such as an increased mortality, multiple organ failure, risk of infection, lung injury and immunomodulation [42,43▪]. The effectiveness of FFP compared with fibrinogen concentrate regarding clinical endpoints as blood loss, transfusion requirements, hospital length of stay, survival and plasma fibrinogen concentration is favorable for fibrinogen concentrates [44]. In patients with massive transfusion, the use of FFP or fibrinogen is indicated according to the European trauma Guidelines. If FFP is used, a plasma : red blood cell ratio of least 1 : 2 is suggested. However, plasma transfusions are to be avoided in patients without substantial bleeding [3▪▪].

In many bleeding situations, including trauma, fibrinogen is the first coagulation factor to become critically low. Early testing for fibrinogen concentration and specially for fibrinogen activity has been proposed and implemented in many centers [3▪▪,35,45–48].

In addition, target levels of fibrinogen concentrations for trauma patients have been defined at 1.5–2.0 g/l in the European Trauma Treatment Guidelines [3▪▪]. As fibrinogen is a central element of hemostasis, achieving these target levels is important. Administering fibrinogen concentrates is advantageous over FFP transfusion because the fibrinogen concentration in FFP is highly variable and rather low with 2 g/l on average [49]. Therefore, large volume transfusions of FFP would be necessary to effectively increase the fibrinogen concentration, and achieving the target fibrinogen concentration of 1.5–2.0 g/l is virtually impossible given the average fibrinogen concentration of 2 g/l. When replacing most FFP transfusions with fibrinogen

Diagnostic	Intervention
Preoperative history 1. Drugs affecting coagulation - Antiplatelet drugs - Heparin - Oral anticoagulation (Vit. K antagonists), Xa antagonists, IIa antagonists 2. Coagulation status? 3. HIT II?	ROTEM after anesthesia induction - Transplant surgery - Cardiac and vascular surgery - Difficult cancer surgery - Liver insufficiency - Intra-abdominal sepsis - Emergency room entry
Blood loss > 50% with diffuse bleeding	
ROTEM analysis - EXTEM, INTEM, FIBTEM, APTEM - HEPTEM in heart and vascular surgery	Target values - Normothermia (temp > 35°C) - Normocalcaemia (Ca > 1.15 mmol/l) - No acidosis (pH > 7.2) - Hematocrit > 0.21 - Hypotension (MAP 55–60 mmHg) **Crystalloid and/or colloid volume substitution**
FIBTEM < 7 mm	Fibrinogen 2–4 g i.v. (maximal 3x2g), after a total of 6 g give FXIII
INTEM (CT and CFT prolonged) and HEPTEM normal or ACT pathological and heparinase ACT normal	Protamine sulfate 1:1 to heparin **crystalloid and colloid volume substitution**
EXTEM/INTEM : Decrease of MCF after maximum was reached **APTEM :** normal ⇨ Hyperfibrinolysis	Tranexamic acid - 15 mg/kg body weight as bolus iv - 1–2 mg/kg/h during surgery iv as perfusion
Ongoing diffuse bleeding	
EXTEM/INTEM MCF < 40 mm CT EXTEM/INTEM normal MCF FIBTEM < 7 mm Hematocrit > 0.21 MCF FIBTEM > 7 mm Platelets < 50 000/ l (< 100 000/ l in cardiac surgery or in patients suffering from traumatic brain injury) **Coagulation test incl. F XIII, F V, INR, PT, aPTT**	Fibrinogen up to 6 g, followed by **Factor XIII** 15 U/kg body weight **crystalloid and colloid volume substitution** **Platelet concentrates** **Target of Factor XIII: > 60% (Factor XIII 15 U/kg body weight)** **Target of Factor V: > 20% (in particular in liver insufficiency /trauma or intra-abdominal sepsis: 2–4 U FFP)**
Ongoing diffuse bleeding	
Quick's value < 30% and Factor V > 20% or EXTEM/INTEM: CT, CFT prolonged	**4 factor prothrombin complex** 1000–2000 IU - Factor II, VII, IX and X Depending on the patients' body weight
In case of massive transfusion	**Target hematocrit 0.21–0.24**
If massive diffuse bleeding continues and	
Treated acidosis Treated hypothermia Treated hypocalcaemia Hematocrit: 0.21–0.24 Excluded DIC Fibrinogen was substituted Platelets > 50 000/ l (> 100 000/ l in cardiac surgery or in patients suffering from traumatic brain injury)	Recombinant factor VIIa 60 g/kg body weight A second dose of 60 g/kg body weight can be given again after 2–4 hours, if bleeding has not completely stopped.

FIGURE 1. Third version of the transfusion algorithm of the University Hospital of Zürich 2013, Switzerland. BW = body weight (modified according to [35], with permission of Lippincott Williams & Wilkins).

concentrate, monitoring factor XIII levels is advisable after the replacement of approximately 50% of the blood volume; in addition, a 60% factor XIII activity level is to be maintained with the administration of factor XIII concentrate [35,50–52].

Apart from single-factor concentrates, prothrombin complex concentrates (PCC) are also part of factor-based algorithms [35,46–48,53,54]. Individual PCCs differ regarding their factors contained, their relative composition, and their thrombotic potential. In general, PCCs are used for the reversal of oral

anticoagulants [55]. The use of PCC is also suggested by the update of the European Trauma Guidelines in 2013 if the initiation of clot formation is prolonged in ROTEM [3▪▪]. PCC should be used only within strict algorithms, the dose should be small and repeat doses should be given with caution to minimize thrombotic risks [54].

Actual studies indicate that a high amount of RBCs, FFPs and platelets can be saved without additional risks for patients by using a coagulation factor concentrate-based coagulopathy management in trauma [56]. Based upon data from four European countries (UK, Germany, Italy and Switzerland), blood substitution and blood products were calculated and found to account for approximately 27% of all costs associated with trauma care on the ICU [57]. The reduced frequency of septic complications and organ failure observed here that translated into trends toward reduced days on ventilator while on ICU and shorter overall in-hospital length of stays may also contribute to cost reduction in acute trauma care without increasing the risk for the individual patient.

DRUGS WITH RENEWED INTEREST

Desmopressin (DDAVP: 1-deamino-8-D-arginine vasopressin, 0.3 mcg/kg) enhances platelet adherence and is the first choice in the treatment of bleeding patients with quantitative deficiency (type 1) and some with qualitative defects (type 2) of von Willebrand factor [58,59]. Patients treated with aspirin, ADP receptor inhibitors such as clopidogrel could benefit from point-of-care testing to assess the individual efficacy of desmopressin treatment [60]. Furthermore, the European Trauma Guidelines suggest that patients treated with aspirin only may benefit from a single dose of desmopressin [3▪▪]. Should the treatment with desmopressin be insufficient, transfusing platelets is the ultimate option. Other antiplatelet drugs such as ticagrelor might not be easily reversed with desmopressin and even platelet transfusion may be relatively ineffective [3▪▪,61▪▪].

NEW DRUGS

New oral anticoagulants acting as direct thrombin (dabigatran) and factor Xa inhibitors (apixaban and rivaroxaban) are now encountered also in the bleeding trauma patient. Experience and treatment options are limited.

There are reports of continuous bleeding after trauma, in emergency surgery and in spontaneous intracerebral hemorrhage [62▪–64▪]. This is probably not because of the higher risk of bleeding *per se* but to the persistence of effective plasma levels of the anticoagulatory substances [65▪].

In healthy volunteers, a high dose (50 U/kg) of nonactivated PCC was able to completely reverse antifactor Xa effects on laboratory parameters due to rivaroxaban [66].

The use of activated factor VII to treat bleeding under new oral anticoagulants is off label. Only ex-vivo and in-vitro studies exist, showing theoretical and limited effect [67,68▪] with case reports of successful hemostatic treatment [69]. Hemodialysis was reported to be effective for dabigatran removal [70▪,71]. Because of the high volume of distribution, Chang *et al.* [72], however, saw a rebound of dabigatran plasma levels after discontinuation of dialysis.

Convincing clinical evidence for the reversal of action of the new oral anticoagulants is lacking; no studies evaluating the clinical success and the possible thrombotic adverse events exist to date. Immediate discontinuation of the anticoagulant is mandatory. Activated charcoal is indicated for the absorption of dabigatran within 2 h after ingestion [73].

Specific antagonists for factor Xa mediated anticoagulation are needed for immediate reversal in the bleeding patient. R-Antidote (PRT064445) may be a potential candidate and is currently under investigation [74].

CONCLUSION

Applying the second pillar of Patient Blood Management to the trauma patient is possible and highly efficacious. Antihyperfibrinolytics such as tranexamic acid, point-of-care testing and coagulation algorithms with the use of factor concentrates allow a reduction of the number of transfusions, the costs and will likely ameliorate outcome of major trauma patients.

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Conflicts of interest

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This article deals with the fact that traumatic injuries worldwide are responsible for over 5 million deaths annually. Bleeding caused by traumatic injury-associated coagulopathy is the leading cause of potentially preventable death among trauma patients. Despite these facts, awareness of this problem is insufficient and treatment options are often unclear. The STOP the Bleeding Campaign therefore aims to increase awareness of this fact and its appropriate management by publishing European guidelines for the management of the bleeding trauma patient, by promoting and monitoring the implementation of these guidelines and by preparing promotional and educational material, organizing activities and developing health quality management tools. The campaign aims to reduce the number of patients who die within 24 h after arrival in the hospital due to exsanguination by a minimum of 20% within the next 5 years.

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Blood transfusions face many issues including questionable safety and efficacy, increasing costs and limited supply. The need to provide effective care for a relatively small population of patients who could not be transfused for various reasons gave rise to 'bloodless medicine and surgery', which was subsequently proposed as a care strategy for all patients, with the goal of minimizing the use of allogeneic blood components. The next evolution came from the shift from a 'product-centred' approach towards a 'patient-centred' approach, that is, a focus on patient outcome rather than use of blood components, which gave birth to 'Patient Blood Management'.

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In the next 5–10 years, blood availability in developed countries will need to increase again to meet the demands of ageing populations. Increasing of the blood supply raises many challenges; new approaches to recruitment and retainment of future generations of blood donors will be needed, and care will be necessary to avoid taking too much blood from these donors. Personalized medicine could be applied to match donors to patients, not only with extended blood typing, but also by using genetically determined storage characteristics of blood components. Growing of red cells or platelets in large quantities from stem cells is a possibility in the future, but challenges of cost, scaling up and reproducibility remain to be solved.

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The authors show that TXA may be successfully given in the prehospital setting without any apparent delays in evacuation. In light of recent evidence, the ability to give TXA closer to the time of wounding represents an important step toward improving the survival of trauma victims with haemorrhage, even before definitive care is available. TXA could be considered a viable option for use by advanced life support providers at or near the point of injury.

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This analysis shows that the early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost effective. Treatment beyond 3 h of injury is unlikely to be effective.

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The authors show by a prognostic model that one can obtain valid predictions of mortality in patients with traumatic bleeding. TXA can be administered safely to a wide spectrum of bleeding trauma patients and should not be restricted to the most severely injured. It has to be evaluated whether or not this model used in clinical practice has an impact on the management and outcomes of trauma patients.

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In this trial, pigs were randomized into three different groups and hemodiluted with hydroxyethyl starch comparing no hemodilution vs. hemoglobin of 4.0 g/dl and vs. the critical hemoglobin level of 2.7 g/dl. In the hemodiluted state 10 mg/kg of pimonidazole was injected, which forms protein adducts in hypoxic cells. Interestingly, metabolic parameters and oxygen consumption did not show that tissue oxygenation was restricted before reaching a hemoglobin level of 2.7 g/dl. Kidneys and skeletal muscle showed enhanced pimonidazole binding and vascular endothelial growth factor expression at a hemoglobin level of 4 g/dl. Other organs like heart, brain and liver showed no signs of tissue hypoxia at hemoglobin levels of 4 g/dl.

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Deep neuromuscular blockade increases the tolerance of acute normovolemic anemia. The underlying mechanism most likely involves a reduction of skeletal muscular oxygen consumption. During acellular treatment of an acute blood loss, neuromuscular blockade might play an adjuvant role in situations in which profound stages of normovolemic anemia have to be tolerated.

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■■ platelet supplementation on platelet aggregability in blood samples from patients treated with acetylsalicylic acid, clopidogrel, or ticagrelor. Br J Anaesth 2013. doi: 10.1093/bja/aet33. [Epub ahead of print]

The authors investigated platelet aggregability with multiple electrode aggregometry with adenosine diphosphate, arachidonic acid and thrombin receptor activating peptide-6 as activators in whole-blood samples from patients treated with ASA, ASA + clopidogrel or ASA + ticagrelor, and from healthy controls. Aggregability was measured before and after supplementation of AB0-compatible fresh apheresis platelets. Platelet supplementation improved platelet aggregability independently of antiplatelet therapy. The effect on ADP-dependent platelet inhibition was limited however. Reduced effect of platelet transfusion is more likely within 2 h of drug intake in patients treated with ASA + ticagrelor compared with ASA + clopidogrel.

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This case presented by the authors shows that the rapid aging of the population increases the likelihood that injured elderly patients will have anticoagulation. The advantages of using dabigatran etexilate instead of warfarin will likely drive widespread use. These phenomena will certainly increase the probability that emergency clinicians will manage an injured patient taking the drug. Acute reversal of the effects of dabigatran etexilate in the actively bleeding patient is a significant challenge. Conventional coagulation studies provide an imperfect assessment of physiology, and data on effective reversal protocols are limited.

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The authors present their experience with three patients who suffered an intracranial hemorrhage either spontaneously or after low-energy cranial trauma and review the available literature describing dabigatran use in patients with traumatic brain injury. Intracranial hemorrhage in patients taking anticoagulants and/or antiplatelets can have either a benign or malignant clinical course. At this time, there is little experience with dabigatran reversal; however, several strategies for rapid reversal have been proposed. All patients with intracranial hemorrhage taking dabigatran should be admitted for close neurological monitoring and serial imaging.

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The authors present a case that suggests that hematoma expansion may occur after novel oral anticoagulants-related intracerebral hemorrhage.

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This study showed that dabigatran is effective in the extended treatment of venous thromboembolism and carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo.

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The new anticoagulants dabigatran and rivaroxaban are responsible for haemorrhagic complications. The authors tested the effect of all putative haemostatic agents on the anticoagulant activity of these new drugs using thrombin generation tests. In an ex-vivo study, 10 healthy white male individuals were randomized to receive rivaroxaban (20 mg) or dabigatran (150 mg) in one oral administration. After a 2 weeks washout period, they received the other anticoagulant. Venous blood samples were collected just before drug administration and 2 h thereafter. Reversal of anticoagulation was tested *in vitro* using PCC, rFVIIa or FEIBA(R) at various concentrations. PCC strongly corrected endogenous thrombin potential-area under the curve (ETP-AUC), whereas rFVIIa only modified the kinetic parameters. FEIBA corrected all parameters. Dabigatran specially affects the kinetics of thrombin generation with prolonged lag-time and time to peak. Although PCC increased ETP-AUC, only rFVIIa and FEIBA corrected the altered lag time. For both anticoagulants, lower doses of FEIBA, corresponding to a quarter to half the dose usually used, have potential reversal profile of interest. Some nonspecific reversal agents appear to be able to reverse the anticoagulant activity of rivaroxaban or dabigatran.

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■ removal in the treatment of acute bleeding: a single center experience. Clin J Am Soc Nephrol 2013; 8:1533–1539.

This study shows that dabigatran concentrations decreased during intermittent hemodialysis but rebounded up within 2 h after the completion of dialysis. Initiation of continuous renal replacement therapy after intermittent hemodialysis attenuated the rebound effect in one patient and contributed to a reduction in dabigatran concentrations of 81% over 30 h. Extracorporeal therapy lowered dabigatran concentrations, suggesting that it removed the drug and may effectively accelerate total clearance, specially in patients with impaired kidney function. The use of prolonged intermittent hemodialysis or intermittent hemodialysis followed by continuous renal replacement therapy is recommended for the management of life-threatening bleeding in patients receiving dabigatran.

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